Impact of Induction Chemotherapy on Estimated Risk of Radiation Pneumonitis in Small Cell Lung Cancer

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Introduction: Induction chemotherapy in patients with bulky small cell lung cancer (SCLC) could lead to decreased tumor burden, smaller radiation fields, and less pulmonary toxicity. This study compared radiation therapy (RT) plans based on pre- and postchemotherapy computed tomography (CT) scans of patients with SCLC to estimate the reduced risk of radiation pneumonitis (RP) after receiving chemotherapy.

Methods: Between 2003 and 2009, 23 patients with stage IV SCLC were treated with chemotherapy alone (no surgery or RT) and had computed tomography scans pre- and post two cycles of platin-based chemotherapy. Simulated RT plans were created as if to deliver 45 Gy to the thoracic disease. The percent of lung receiving ≥20 Gy (V20), mean lung dose, and normal tissue complication probability (NTCP) was evaluated in patients who had a partial response (≥30% volumetric reduction) in gross tumor volume.

Results: One (4.3%) patient had a complete response, 18 (78.3%) had a partial response, and four (17.4%) had stable disease. Among 18 responders, the absolute decrease in V20 was 7.4% ($p < 0.01$), in mean lung dose was 3.3 Gy ($p < 0.01$), and in NTCP was 5.5% ($p < 0.01$). Patients with a prechemotherapy V20 ≥35% versus V20 less than 35% had an average absolute reduction in NTCP of 10% versus 2% ($p < 0.01$).

Conclusion: Patients with limited stage SCLC with a V20 ≥35% may benefit from induction chemotherapy as there is an estimated reduction of RP of 10%. This reduction in risk of RP after induction chemotherapy should be weighed against risks and benefits of delaying upfront RT.

Key Words: Radiation pneumonitis, Small cell lung cancer, Chemotherapy response.

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An estimated 223,520 people in the United States will be diagnosed with lung cancer in 2010,[1] of which 15 to 25% will be small cell lung cancer (SCLC) histology. Patients with SCLC can be staged using the TNM staging system, but in practice, these tumors are divided into those with limited (LSCLC) versus extensive (ESCLC) stage disease[2] based on a simple staging system developed by the Veterans Administration Lung Study Group in 1957 for randomized trials in inoperable patient with lung cancer.[3] Approximately one third of patients will present with LSCLC.[4] LSCLC is defined as disease confined to the thorax that can be included in a "tolerable" radiation field, whereas extensive stage patients often have extrathoracic metastases.[3]

Although early thoracic radiation therapy (TRT) with chemotherapy has been found to have a survival benefit in some trials,[5–7] yet not in others,[8–12] the standard treatment for patients with LSCLC can still be considered chemotherapy with TRT starting day 1 of the first cycle of chemotherapy.[13–15] In patients with bulky tumors, this can lead to a large volume of normal lung receiving radiation, often increasing the chance of treatment-related radiation pneumonitis (RP). Previous studies have shown that the volume of normal lung receiving ≥20 Gy (V20), mean lung dose (MLD), and location of tumor are predictive factors for developing clinically evident (grades 2–3) pneumonitis.[16–19] Therefore, some parameters that have been used to define a "tolerable" radiation field include V20 and MLD.

An alternative is to treat patients with LSCLC with induction chemotherapy followed by concurrent chemoradiation therapy. When cisplatin-containing regimens are used in ESCLC, the overall response rate by RECIST is approximately 40 to 70%,[20,21] and complete response (CR) rate is estimated at 10 to 20%. So we hypothesized that induction chemotherapy for LSCLC would allow time for tumor response that could lead to smaller radiation fields that would allow for decreased V20 and MLD, decreased incidence of pulmonary toxicity, and the ability to allow for higher doses of radiation to maximize the probability of local control.[22,23] Currently, there is limited information about the effect of induction chemotherapy on the volume of normal lung subsequently irradiated, i.e., the volume of normal lung that can be spared by allowing for tumor response to induction chemotherapy.

The objective of this study was to estimate the reduction in risk of pneumonitis, using simulated RT plans on the pre- and post two cycles of chemotherapy computed tomography (CT) scans in patients with ESCLC who did not get

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thoracic radiation or resection, by measuring the change in V20, MLD, clinical target volume (CTV), and normal tissue complication probability (NTCP).

PATIENTS AND METHODS

A retrospective review of consecutive patients identified by the Tumor Registry at the University of Colorado from 2003 to 2009 identified 23 patients with ESCLC who received chemotherapy (no surgical resection or radiation) and had pre and postchemotherapy diagnostic CT scans. Two cycles of chemotherapy were given between the CT scans. Patients with pleural effusions were excluded.

The XIO Radiation planning system (Elekta CMS, St. Louis, MO) was the treatment planning system used to measure the volumetric changes in gross tumor volume (GTV) and to create simulated radiation plans on diagnostic CT scans performed pre- and post two cycles of chemotherapy. Plans were only made for patients who had a volumetric decrease of GTV ≥30% or partial response (PR). The definitions for response that were used include a complete responder (CR) had no residual tumor, partial responder had ≥30% decrease in GTV, a patient with progressive disease had ≥24% increase in GTV, and stable disease was defined as less than 30% reduction and less than 24% increase in GTV.[24]

Critical structure dose constraints were defined using the definitions from the CALGB 30610/RTOG 0538 protocol[25] (Table 1). The target volumes are summarized in Table 2. CTV was defined as GTV plus elective nodal coverage of the ipsilateral hilum and subcarina. The planning target volume (PTV) was created after a 1.5 cm expansion in the superior and inferior direction and a 1 cm expansion axially. Differentiating tumor from atelectasis is always an issue. A senior radiation oncologist reviewed all volumes, and IV contrast-enhanced CT scans helped distinguish tumor from atelectasis. Positron emission tomography scans were not routinely available to help delineate tumor volumes from atelectasis. For each patient, a three-dimensional plan (3D) was first generated. If the 3D plan did not satisfy the constraints, an intensity modulated radiation therapy (IMRT) plan was generated. The same type of plan (i.e., 3D or IMRT) was created using the pre- and postchemotherapy CT scans with similar beam angles and beam energies. As the CT scans used were diagnostic scans, they often had portions of the skin cutoff near the shoulder regions. This cutoff portion was treated as the patient's skin as it was not possible to draw in skin. The density correction for contrast was also used for the diagnostic scans that used contrast. Dose calculations with inhomogeneity corrections for lung were performed. All plans had a minimum of 95% of the PTV receiving the prescription dose. A dose-volume histogram was created to measure and compare the doses to organs at risk (spinal cord, heart, esophagus, and normal lung) and the following parameters between pre- and postchemotherapy RT plans: lung V20, MLD, GTV, CTV, and PTV.

The Lyman-Kutcher-Burman (LKB) NTCP model[26,27] was used to predict the risk of RP, the end point for lung normal tissue toxicity to irradiation. The NTCP was calculated using the tools provided in the treatment planning system. The NTCP model uses the following information to estimate the incidence of normal tissue complication: dose-volume histogram data of the irradiated normal structures, tolerance dose for these structures, fitted parameters describing slope of the NTCP curve, and fractional volume dependence for organs. The parameters needed to calculate NTCP included the anatomical structure, TD50 (Gy), n (volume dependency of the organ), and m (slope of the NTCP curve). Values of TD50 = 31.4 Gy, n = 1, and m = 0.45 were used based on the recent QUANTEC recommendations for lung tissue.[28]

The Bradley nomogram[17] is another model that estimates the probability of pneumonitis, or NTCP, by using the MLD and the center of mass (COM) of the GTV. We also used the Bradley nomogram[17] to predict the probability of pneumonitis. The superior/inferior location of tumor within lung was calculated by extrapolating from methods described by Bradley et al. As only the superior/inferior location was found to be predictive of pneumonitis, this is the only dimen-

TABLE 1. Critical Structure Dose Constraints from the CALGB 30610/RTOG 0538 Protocol

Critical Structure	Dose Constraint
Spinal cord	Total "direct" + "scatter" max dose <41 Gy
Lung	• Volume of bilateral lung minus CTV receiving ≥20 Gy (V20) ≤40% • Mean lung dose (MLD) ≤20 Gy
Esophagus	Mean dose <34 Gy if possible (not absolute constraint)
Heart	60 Gy to <1/3, 45 Gy to <2/3, 40 Gy to <100% of the heart

CTV, clinical target volume.

TABLE 2. Treatment Volume Definitions Based on CALGB 30610/RTOG 0538 Protocol

Target Volumes	Definition
Gross tumor volume (GTV)	Volume occupied by visible or palpable disease as seen on CT/MRI, FDG-PET imaging, or biopsy-positive sites.
Clinical target volume (CTV)	GTV plus any sites that warrant irradiation because of potential occult tumor involvement, including ipsilateral hilum (level 10), subcarinal disease (level 7). No elective treatment of supraclavicular fossae or bilateral mediastinal lymph nodes (levels 3, 4R, 4L, 5, and 6).
Planning target volume (PTV): standard CT simulation without 4DCT	CTV plus 1.5 cm (superior-inferior direction) and 1.0 cm (axial) margin added in to compensate for variability in treatment setup, breathing, and motion during treatment.

CT, computed tomography; MRI, magnetic resonance imaging; FDG, fluorodeoxyglucose; PET, positron emission tomography.

TABLE 3. Patient Characteristics

Age (n = 23)	
Median (yr)	64
Range (yr)	46–83
≤65 yr (%)	61% (14/23)
>65 yr (%)	39% (9/23)
Sex	
Male	65% (15/23)
Female	35% (8/23)
Chemotherapy	
Carboplatin/etoposide	52% (12/23)
Cisplatin/etoposide	22% (5/23)
Carboplatin/irinotecan	17% (4/23)
Cisplatin/etoposide + carboplatin/etoposide	4% (1/23)
Carboplatin/paclitaxel	4% (1/23)
Center of mass (COM)	
Upper	13% (3/23)
Middle	43% (11/23)
Lower	39% (9/23)

TABLE 4. Tumor Response to Two Cycles of Chemotherapy

Total no. of patients	23
Complete response	1 (4.3%)
Partial response	18 (78.3%)
Stable	4 (17.4%)
Progressed	0

Response data for all 23 patients. Partial response is defined as a volumetric decrease in gross tumor volume (GTV) of ≥30%. Stable disease was defined as <30% reduction and <24% increase in GTV, whereas progression was >24% increase in GTV.

sion calculated. The entire length of the lung was first measured and normalized to continuous values ranging from 0 to 1 inferior-to-superior direction. The center of the GTV along the superior-inferior axis within the lung parenchyma was then measured and assigned a value between 0 and 1 (with 1 being the most superior location and 0.5 being midlung). Locations were separated into upper (>0.75), middle (0.5–0.75), and lower (<0.5) lung. The MLD calculated from the pre- and postchemotherapy plans, along with the upper, middle, or lower location of the tumor, was used to predict the probability of pneumonitis using the Bradley nomogram.

RESULTS

Patient characteristics are summarized in Table 3. Among the total 23 patients, 19 (82.3%) patients were defined as responders as they had a CR or PR, defined as ≥30% reduction in volumetric CTV, after two cycles of platin-based chemotherapy. Only one (4.3%) patient had a CR; however, because of the patient's complication of a broncho-pleural fistula, simulated radiation plans were not made for this patient. Four (17.4%) other patients had stable disease and, therefore, were not analyzed further with simulated radiation plans. The response data are summarized in Table 4, and the absolute and relative decrease in CTV of all 23 patients is shown in Figure 1.

Among the 18 responders for whom pre- and postchemo RT plans were created, the mean prechemotherapy, postchemotherapy, absolute decrease, and relative decrease were measured for the CTV, V20, MLD, and NTCP. The mean CTV decreased from 338.3 ml (88.1–1570 ml) to 85.7 ml (5.95–354.2 ml) reflecting a 252.5 ml (18.9–1384.5 ml) absolute decrease or a 70% (30–93%) relative reduction in tumor and elective lymph node burden. The mean lung V20 decreased from 33.9% (17.7–70.6%) to 26.5% (16.7–36.5%) reflecting a 7.4% (−6.6 to 34%, $p < 0.01$) absolute decrease or a 17% (−37 to 54%) relative reduction in V20. The MLD decreased from 17.1 Gy (11.5–29.2 Gy) to 13.8 Gy (10.4–19.3 Gy) reflecting a 3.3 Gy (−0.13 to 12.1 Gy, $p < 0.01$) absolute decrease or an 18% (−1 to 43%) relative reduction in MLD. The mean lung NTCP decreased from 16.5% (6.98–44%) to 11% (6.1–19.7%) reflecting a 5.5% (−0.1 to 28.5%, $p < 0.01$) absolute decrease or a 28% (−1 to 65%) relative reduction in NTCP. The absolute estimated risk of pneumonitis ≥ grade 2 was decreased by ≥5% in seven (30%) patients and by ≥10% in two (8.7%) patients, whereas the relative risk was decreased by ≥20% in 13 (57%) patients and by ≥30% in eight (34.8%) patients. Figure 2 graphically shows the absolute and relative change in NTCP for the 18 patients in whom RT plans were created. Patients 1 to 4 did not have ≥30% volumetric reduction, and patient 23 had a CR, but because of a broncho-pleural fistula in his postchemotherapy scan, we did not create RT plans for that patient. Table 5 presents a summary of data.

A representative case of the benefit from two cycles of chemotherapy can be seen in patient 5 displayed in Figure 3. This patient would not have been a good candidate for radiation at the time of diagnosis given the anticipated high risk of RP. Nevertheless, the plan based on the postchemotherapy scan offered a safer RT plan.

The absolute and relative decrease in V20 and NTCP after two cycles of chemotherapy was greater for patients with a higher prechemotherapy V20 (Table 6). Using SWOG0023 trial's observation that there was a correlation of V20 more than 35% with significant treatment-related pneumonitis, we grouped our patients using V20 ≥35% as a cutoff. For patients with a prechemotherapy V20 ≥35%, the NTCP was decreased by 10%, whereas for patients with V20 less than 35%, the absolute reduction in NTCP was only 2% ($p < 0.01$). These results maintained significance even when an outlier patient with a prechemotherapy V20 of 70% was removed from the analysis. It is also important to notice that although the prechemotherapy V20, MLD, and NTCP were significantly different between the two groups of patients with V20 more than or less than 35%, after two cycles of chemotherapy this difference was no longer significant.

As depicted earlier (Figure 1), there was a significant response in CTV to chemotherapy. Although the average prechemotherapy CTV of the patients with prechemotherapy V20 more than 35% was almost double the average CTV in patients with a prechemotherapy V20 less than 35%, this was not statistically significant (Table 6). Although one would

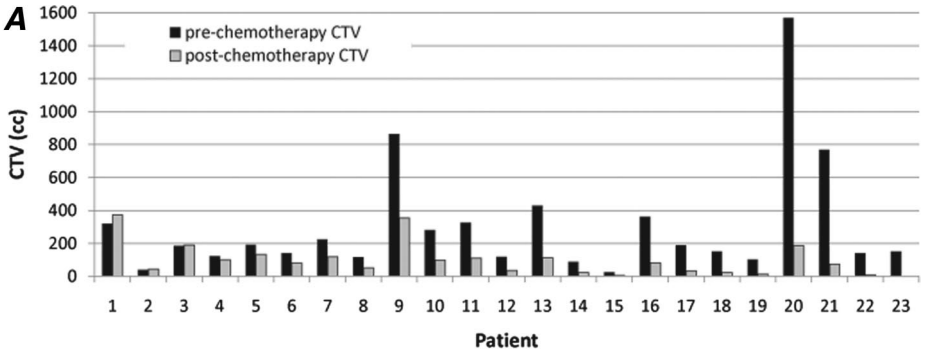

FIGURE 1. *A,* Absolute change in clinical target volumes (CTV) and (*B*) relative change in CTV (ml) between pre- and post two cycles of chemotherapy computed tomography (CT) scans for all 23 patients.

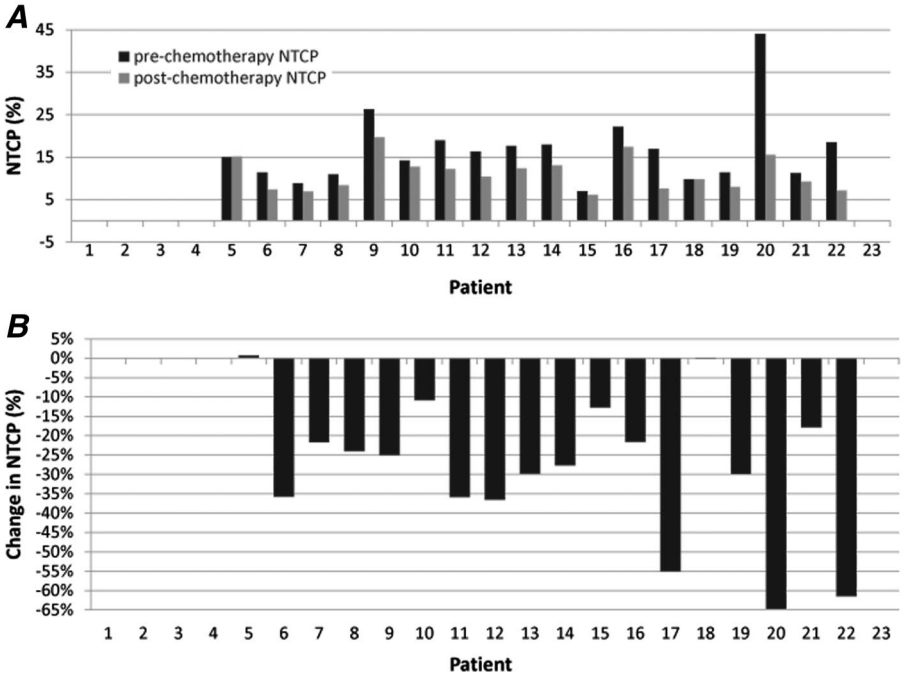

FIGURE 2. *A,* Absolute change in normal tissue complication probability (NTCP) and (*B*) relative change in NTCP (%) between prechemotherapy and postchemotherapy computed tomography (CT) scans for 18 patients who had ≥30% decrease in gross tumor volume (GTV) and for whom pre and postchemotherapy simulated radiation therapy plans were created. Patients 1 to 4 did not have ≥30% reduction in GTV, and patient 23 had a complete response (CR), but because of postchemotherapy bronchopleural fistula, RT plans were not created.

expect a larger CTV to correlate to a larger lung V20, there are times when a low tumor burden also results in higher V20 values. This is mainly due to a peripheral tumor location as there is a larger volume of normal lung that receives radiation. As displayed in Figure 4, patient 14 had a prechemotherapy CTV of 88.1 ml (which was the second to lowest among all the patients in this study), but the V20 was 36.4% (7th highest V20). The tumor was located along the left posterior peripheral lung. After two cycles of carboplatin and etoposide, the CTV decreased by 74% from 88.1 to 22.8 ml and the V20 decreased by 20% from 36.4 to 29.1%. This example reiterates that both the tumor burden and location of the tumor affect V20.

In keeping with the Bradley nomogram, the probability of pneumonitis, or NTCP, for tumors located in the lower lung not only had a high initial risk but also had a greater degree of improvement in NTCP, when compared with tumors in the middle or upper lung (Table 7). The Bradley

TABLE 5. Summary of Volumes and Radiation Parameters in Pre- and Postchemotherapy Radiation Plans for the 18 Eligible Responders

	CTV	PTV	MLD	V20	NTCP
Mean prechemotherapy	338.3 ml (88.1–1570 ml)	971.3 ml (213.0–3413.6 ml)	17.1 Gy (11.5–29.2 Gy)	33.9% (17.7–70.6%)	16.5% (6.98–44.0%)
Mean postchemotherapy	85.7 ml (5.95–354.2 ml)	444.5 ml (129.1–1340.3 ml)	13.8 Gy (10.4–19.3 Gy)	26.5% (16.7–36.5%)	11.0% (6.1–19.7%)
Mean absolute decrease	252.5 ml (18.9–1384.5 ml)	526.8 ml (65.8–2682.5 ml)	3.3 Gy (−0.13 to 12.1 Gy) $p < 0.01$	7.4% (−6.6 to 34%) $p < 0.01$	5.5% (−0.1 to 28.5%) $p < 0.01$
Mean relative decrease	70% (30 to 93%)	48% (11 to 79%)	18% (−1 to 43%)	17% (−37 to 54%)	28% (−1 to 65%)

Data from 18 responders for whom pre- and postchemotherapy radiation plans were created, including the mean absolute decrease in clinical target volume (CTV), planning target volume (PTV), mean lung dose (MLD), percent of lung receiving ≥20 Gy (V20), and predicted risk of pneumonitis as calculated by the Lyman–Kutcher–Burman (LKB) model for normal tissue complication probability (NTCP).

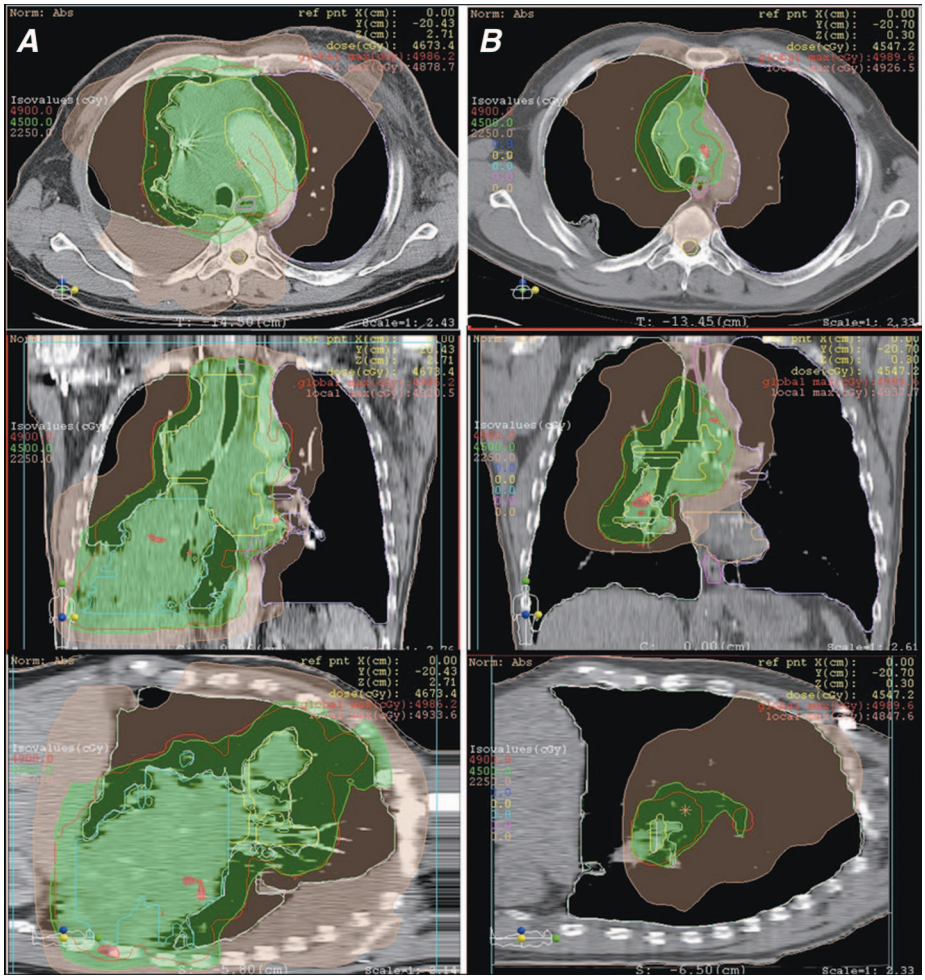

FIGURE 3. Simulated radiation therapy (RT) plans of patient 5 displayed in axial, coronal, and sagittal views on the (*A*) prechemotherapy and (*B*) postchemotherapy computed tomography (CT) scans. This is an example of how chemotherapy reduced tumor volume allowed for a safer RT plan. The percentage of lung receiving >20 Gy (V20) decreased from 71 to 36%, the normal tissue complication probability (NTCP) decreased from 44 to 16%, and mean lung dose (MLD) decreased from 29 to 17 Gy as the clinical target volume (CTV) decreased from 1570 to 186 ml, and the normal lung volume increased from 4376 to 7029 ml. Green represents 45 Gy (100% isodose), red represents 49.5 Gy (110% isodose), and brown represents 22.5 Gy (50% isodose).

nomogram NTCP was improved by 10% in the lower lung tumors compared with 3% in the middle and upper lung tumors ($p < 0.04$). These results were also seen when using the LKB model for NTCP; however, the degree of absolute improvement in NTCP was not statistically significant.

Although most of the patients who had more than 30% volumetric reduction in GTV also had an improvement in V20 after two cycles of chemotherapy, Figure 5 displays patient 3 who actually had a 37% relative increase in V20 from 17.7 to 24.3% likely due to the significant amount of previously atelectatic lung that reinflated after chemotherapy.

DISCUSSION

Our study found a statistically significant improvement in the volume of normal lung receiving ≥20 Gy (V20), MLD, and NTCP that predicts for RP in patients with ESCLC after two cycles of platin-based chemotherapy based on simulated RT plans on pre and postchemotherapy CT scans.

TABLE 6. Comparison of Dosimetric Parameters When Separated by Prechemotherapy V20 ≥ or <35%

	V20 ≥35%	V20 <35%	*p*
No. of patients	8	10	
V20			
Mean prechemotherapy	42%	27%	<0.01
Mean postchemotherapy	29%	25%	NS
Absolute reduction	14%	2%	<0.01
Relative reduction	31%	6%	<0.01
NTCP			
Mean prechemotherapy	22%	12%	<0.01
Mean postchemotherapy	12%	10%	NS
Absolute reduction	10%	2%	<0.01
Relative reduction	42%	17%	<0.01
MLD			
Mean prechemotherapy	20 Gy	15 Gy	<0.01
Mean postchemotherapy	15 Gy	13 Gy	NS
CTV			
Mean prechemotherapy	466 ml	236 ml	NS
Mean postchemotherapy	108 ml	68 ml	NS

The average pre- and postchemotherapy values of the percent of lung receiving ≥20 Gy (V20), mean lung dose (MLD), and normal tissue complication probability (NTCP), clinical target volume (CTV), and the absolute and relative reduction in these parameters in patients separated into groups based on prechemotherapy V20 > or <35%.

NS, not significant.

Although patients with limited SCLC are often treated with radiation starting concurrent with the first cycle of chemotherapy using a standard radiation schedule delivering 1.5 Gy per fraction twice a day to 45 Gy,[14,29] there are patients who present with a large amount of thoracic disease who may initially be deemed too "extensive" to safely treat with upfront chemoradiation.[3,14] There have been several randomized trials addressing the timing of thoracic RT; some trials report a survival benefit,[5–7] whereas others do not.[8–12] A meta-analysis analyzed these eight trials and concluded that although there is a possible benefit of early thoracic RT on 5-year OS, more research is needed to determine the optimal timing of chest RT, especially in relationship to type of chemotherapy, volumes treated, and compliance (or ability to complete treatment).[30] Several of these controversies will hopefully be addressed by the ongoing studies such as the "Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Small Cell Lung Cancer also Receiving Cisplatin and Etoposide" (CALGB 30610/RTOG 0538)[25] and the Concurrent ONce daily VErsus twice daily RadioTherapy (CONVERT) study (C. Faivre-Finn, Christie Hospital, Manchester, UK, personal communication). CONVERT is a phase III study comparing 45 Gy twice daily with 66 Gy daily to known disease only (no elective nodal irradiation), starting with the second cycle of four to six cycles of cisplatin-etoposide chemotherapy. CALGB 30610/RTOG 0538, an intergroup study in North America, is comparing 3 dose/fractionation schedules with elective nodal irradiation.

The best dosimetric parameter to predict radiation-induced lung toxicity is still not known[28,31]; however, previous studies have shown that in patients with non-small cell lung cancer (NSCLC) who were treated with conventional once daily radiotherapy, the V20, MLD, NTCP, and location of tumor are predictive factors for developing clinically evident (grades 2–3) pneumonitis.[16–18,32–38] The Southwest Oncology Group (SWOG) 0023 trial also observed the correlation of V20 more than 35% with significant treatment-related pneumonitis and significantly worse median survival in NSCLC.[39] Our results suggest that in patients with SCLC in whom two cycles of chemotherapy could decrease their volumetric tumor burden by more than 30%, the absolute risk for RP ≥ grade 2 can be decreased by an average of 5.5%; approximately 30% of patients could have a ≥5% reduction in NTCP, and 8 to 9% patients could have ≥10% reduction in NTCP. The benefit of chemotherapy is even more pronounced in those patients who would have had a prechemotherapy V20 more than 35%; the absolute risk of RP is decreased by 10% compared with only 2% in patients with prechemotherapy of V20 less than 35%.

As our study is a simulated analysis of RT plans for patients with SCLC on their pre- and postchemotherapy diagnostic scans, we applied information from well-established models and parameters to estimate RP. The MLD model was shown to correlate to both the empirical model proposed by Kutcher and Burman[27] and a radiobiological model developed by Niemierko and Goitein[40] and Jackson et al.[41] used to predict pneumonitis.[36] In the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) publication on radiation dose-volume effects on the lung,[28] a logistic regression was fitted to RP versus MLD data from 10 published studies. Our results for MLD and LKB-NTCP data fit nicely onto this logistic fit. Other studies, similar to Bradley et al.,[17] have shown that both the MLD and the location of the tumor better predicted RP than MLD alone.[17,18] We showed that our patients with lower lung COM tumors had a significantly higher prechemotherapy NTCP and greater benefit from two cycles of chemotherapy than those with middle or upper COM tumors.

Although most of the studies that have evaluated RP and TRT were based on conventional once daily radiotherapy in NSCLC, there were several studies that compared RP in accelerated hyperfractionated thoracic radiotherapy (AHFRT) to conventional once daily radiotherapy (QDRT) for LSCLC.[42–46] Tsujino et al.[19] specifically studied the relationship between lung V20 and the development of RP in 43 patients with LSCLC treated with concurrent chemotherapy and radiation delivered at 1.5 Gy per fraction twice daily to 45 Gy over 3 weeks, the same fractionation we used in our simulated RT plans. Multivariate analysis, which included multiple radiation dosimetric end points, age, forced expiratory volume and gender, revealed that only V20 significantly predicted for subsequent RP ≥ grade 2. Twelve-month cumulative incidence of grade 2 or higher RP according to lung V20 values for the AHFRT group was 0% ($n = 6$), 7.1% ($n = 14$), 25% ($n = 16$), and 42.9% ($n = 7$) in patients with a V20 of less than 20%, 21 to 25%, 26 to 30%, and more than 30%, respectively.

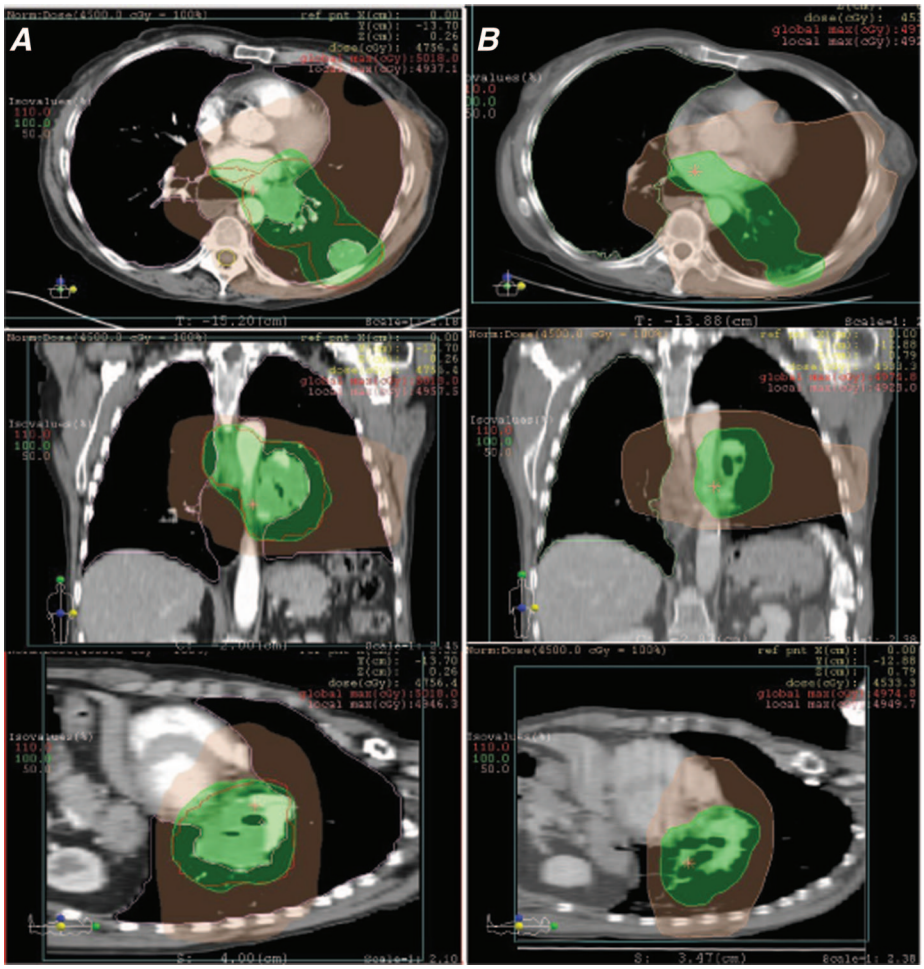

FIGURE 4. Simulated radiation therapy (RT) plans of patient 14 displayed in axial, coronal, and sagittal views on the (*A*) prechemotherapy and (*B*) postchemotherapy computed tomography (CT) scans. Notice the amount of normal lung being irradiated due to the peripheral location of the tumor. Green represents 45 Gy (100% isodose), red represents 49.5 Gy (110% isodose), and brown represents 22.5 Gy (50% isodose).

TABLE 7. Normal Tissue Complication Probability (NTCP) Values Derived from the Bradley Nomogram and Lyman–Kutcher–Burman (LKB) Model

	All Patients	Lower COM	Middle/Upper COM	*p*
No. of patients	18	9	9	
Bradley nomogram NTCP				
Mean prechemotherapy	26%	36%	16%	<0.01
Mean postchemotherapy	20%	26%	13%	<0.01
Absolute difference	6%	10%	3%	<0.04
Relative difference	25%	27%	20%	NS
LKB-NTCP				
Mean prechemotherapy	17%	20%	13%	<0.05
Mean postchemotherapy	11%	13%	10%	0.06
Absolute difference	6%	7%	3%	NS
Relative difference	33%	37%	28%	NS

The estimated risk for radiation pneumonitis in pre- and postchemotherapy scans for the 18 patients who had ≥30% reduction in gross tumor volume (GTV) when patients were separated based on the location of the center of mass (COM) of the tumor.

By applying the estimates from the findings of Tsujino et al. on our study's set of 18 patients with SCLC in whom the mean lung V20 statistically significantly decreased from 34 to 27% after two cycles of induction chemotherapy, the predicted 12-month cumulative incidence of grade 2 or higher RP decreased from 42.9 to 25%. These estimates of RP are more than double the estimates from the NTCP values derived from the LKB model, which calculated a decrease in NTCP from 16.5 to 11%. The upper limit of V20 in the study by Tsujino et al. was 35%, whereas eight (44%) of our patients had a prechemotherapy V20 greater than 35%, and one patient continued to have a V20 more than 35% in the postchemotherapy RT plan. It is likely that as our patients had higher V20 values than the patients analyzed in the study by Tsujino et al., our data points would have been skewed toward the higher end of risk for RP.

Our data fit more closely to the the LKB model than to the findings of Tsujino et al., even though the LKB model may apply more closely to patients receiving daily fractionation than to twice daily fractionation that is often still used in SCLC. When Tsujino et al. compared rates of RP in patients given QDRT versus AHFRT, the V20 values tended to be higher for the same grade of RP in the AHFRT group than in the QDRT group. So it is possible that the LKB model may even overestimate the risk of RP in patients who get twice daily RT.

There were 19 of the 23 patients (83%) who had a CR or PR to two cycles of chemotherapy; a response rate which

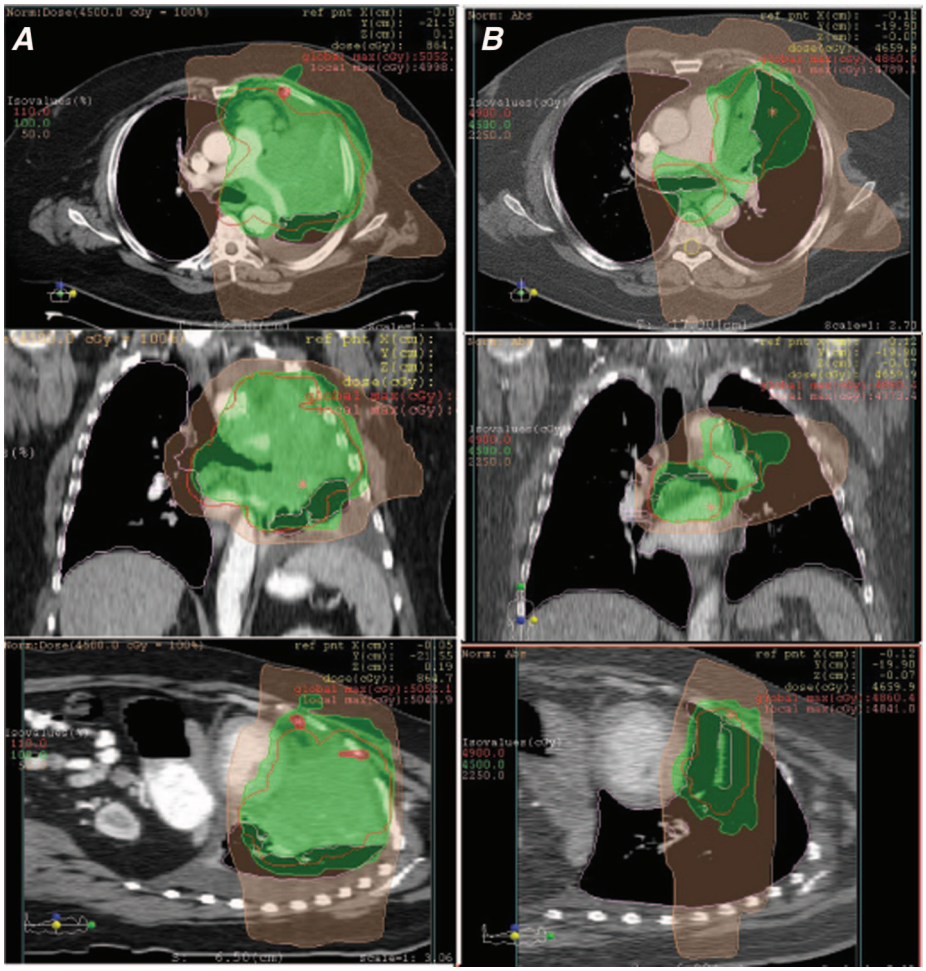

FIGURE 5. Simulated radiation therapy (RT) plans of patient 3 displayed in axial, coronal, and sagittal views on the (*A*) prechemotherapy and (*B*) postchemotherapy computed tomography (CT) scans. The left lung volume expanded from 270 to 1861 ml, whereas the percentage of lung receiving >20 Gy (V20) increased 37% from 17.7 to 24.3%, likely due to the reinflation in normal lung. Green represents 45 Gy (100% isodose), red represents 49.5 Gy (110% isodose), and brown represents 22.5 Gy (50% isodose).

is slightly higher than previously reported SCLC response rates of 40 to 70% to induction chemotherapy.[20,21,47] During the time these patients were treated, it was the usual medical practice at our institution to rescan after two cycles of chemotherapy. Oncologists may consider checking tumor response after one cycle of chemotherapy to assess whether the tumor volumes have decreased sufficiently to start concurrent RT. This is also the study design in the CONVERT study mentioned earlier in the text.

As there can be a large difference between prechemotherapy or postchemotherapy volumes, it is important to define what volumes will be used for radiation planning purposes. It is now standard practice to use the postchemotherapy volumes.[14] An earlier study by Liengswangwong et al.[48] tried to determine the most appropriate volume that should be encompassed by TRTs for patients with LSCLC who have responded to initial chemotherapy. This retrospective study of 59 patients with SCLC found that the use of TRT fields that encompass postchemotherapy tumor volumes did not decrease treatment efficacy: it did not increase the risk of marginal failures or intrathoracic failures outside the TRT field. Nevertheless, they could not clearly depict if this reduction in volume of irradiated normal lung decreased the risk of developing RP. This study supports our decision to use postchemotherapy volumes.

The decision to use elective nodal irradiation was consistent with those used in the CALGB/RTOG protocol.[25] One deviation from this protocol was that only the ipsilateral hilum and subcarina were electively covered, whereas the protocol asked for additional elective coverage of the ipsilateral mediastinum. Although there is evidence that involved field irradiation is just as effective as using elective coverage,[49,50] the use of elective coverage of the ipsilateral hilum and subcarina continues to be common clinical practice for patients with SCLC. Elective coverage of lymph nodes would increase the "absolute" V20, MLD, and NTCP, especially in the contralateral lung when trying to cover the subcarinal region. Nevertheless, it would not necessarily change the relative change, pre- and postchemotherapy, in these parameters.

Although V20, MLD, and NTCP are often reliable parameters with which to analyze whether a radiation plan offers a tolerable risk of pneumonitis, there are situations when these values may be less helpful. For example, when a tumor compresses an airway and causes atelectasis, or collapse of part of the lung, it may be difficult to determine what

part of the consolidation is tumor and what part is normal collapsed lung.[51,52] If the tumor and collapsed lung are all contoured as the CTV, then the calculations for V20, MLD, and NTCP may have spurious results. Figure 5 displays a prechemotherapy scan of patient 3, which shows a large consolidation in the left lung. In the postchemotherapy scan, the left lung largely reinflates from 270 to 1680 ml. By relying on the V20 results alone, one would think that the postchemotherapy RT plan resulted in a V20 that was relatively 37% worse than the prechemotherapy scan. Nevertheless, in this case, we can clearly see that the chemotherapy improved the patient's scans, and the postchemotherapy scan would be more ideal for an RT plan. The increasing use of positron emission tomography scans may help to further delineate tumor from atelectasis.[53]

In conclusion, our results suggest that patients with LSCLC with a V20 ≤35% had only a 2% decreased risk in RP, indicating that starting chemoradiation immediately is advisable. Nevertheless, patients with LSCLC with a V20 more than 35% may benefit from induction chemotherapy as there is an estimated reduction of RP of 10%. This reduction in risk of RP after induction chemotherapy should be weighed against risks and benefits of delaying upfront RT.

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